HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on August 14, 2020 via webinar. The meeting was called to order by Dr. Moron, Interim Chair at 9:34 a.m.

Members

Member Names	Attendance	Member Names	Attendance
Yekini Adeyemi, RN	Present	Glenn Shipley, DO	Absent
Angela Babin, RPh	Present	Lesia Trickett, MD	Present
Jean Baemayr, PharmD- Secretary	Present	Ashton Wickramasinghe, MD	Present
John Bennett, MD	Present		
Bonnie Burroughs, RPh	Present	Tim Bray (non-voting)	Absent
German Corso, MD	Present	Brad Fitzwater, MD (non-voting)	Absent
Catherine Hall, PharmD	Present	Connie Horton, APRN (non-voting)	Absent
Jeanna Heidel, PharmD	Present	Raul Luna, RN (non-voting)	Absent
Dana Hopkins, RN	Present	Mike Maples (non-voting)	Absent
Jeffery Matthews, MD	Absent	Nina Muse, MD (non-voting)	Absent
David Moron, MD- Interim Chair	Present	Peggy Perry (non-voting)	Absent
Kenda Pittman, PharmD	Present	Rachel Samsel, (non-voting)	Absent
Rishi Sawhney, MD	Present		

Guests Present: Barbara Beadles, MD, Kerrville State Hospital; Guy Campbell, PharmD, HSCS State Supported Living Centers; Rania Kattura, PharmD, Austin State Hospital; Lisa Mican, PharmD, Austin State Hospital; Erendira Orozco, MD, Resident, Rio Grande State Center; Brittany Parmentier, PharmD, UT Health East Texas; Ann Richards, PharmD, HSCS State Hospitals.

Opening

Introduction and Other Information

Dr. Messer has left the committee in order to perform the duties of superintendent and medical director at Terrell State Hospital. Dr. Moron will be assuming the role of interim chairman of this committee.

Yekini Adeyemi, RN (Ade) and Lesia Trickett, MD have been appointed to the committee as nurse and physician representatives for the state supported living centers, respectively. Dana Hopkins, RN was introduced as the new nurse representative for the state hospitals. Dr. Beadles was introduced as the interim chief medical officer for the state hospitals, replacing Dr. Muse who is retiring.

Conflict of Interest Disclosures

The committee members present did not disclose any new conflicts.

Review of Minutes

The minutes from the April 17, 2020 meeting were approved as previously distributed.

The committee agreed that, in the interest of efficiency, the names of the committee members putting forth motions and seconding motions were not necessary to be included in the minutes. The committee will still generally follow Robert's Rules of Orders while conducting the meetings.

Unfinished Business

TAC Title 25, Part 1, Chapter 415, Subchapter C (April 2017)

The proposal packet is being routed through the various stages of approval. Upon legal review, it was determined that Local Intellectual and Developmental Disabilities Authorities (LIDDAs) should be included. The Texas Council of Community Centers also recommended that LIDDAs be referenced in the new rules. The revised rules are scheduled to be presented to the HHSC Executive Council on August 20. The anticipated rule effective date is January 2021.

New Business

Adverse Drug Reaction Reports

The committee discussed four adverse drug reaction reports that were received from the field. These adverse events were reported to the FDA's MedWatch program.

ADR: valbenazine/ akathisia

A 35-year-old Hispanic male with a long history of tardive dyskinesia was started on valbenazine (Ingrezza®) 40 mg oral daily in the morning on 1/28/20. The dose was increased to 80 mg oral daily in the morning on 2/4/20. On 2/5/20 at 5:49 PM, the patient was prescribed propranolol 10 mg oral three times daily for akathisia. On 2/18/2020, the attending verbally stated that the patient's akathisia was likely attributable to valbenazine as this is a known side effect.

On 3/2/2020 it was noted that the patient had been refusing to have his vital signs taken therefore propranolol was not being given. The attending noted that the patient usually receives as needed diphenhydramine which is helpful in mitigating anxiety. The patient's propranolol was increased from 10mg oral three times daily to 20 mg oral three times daily, then reduced on 3/3/2020 to 20mg oral twice daily.

On 3/4/2020 at 2:45 PM, the patient was observed to be demonstrating odd behavior and complaining of anxiety. Vital signs, CRP, troponin, and CBC were within normal limits. An EKG showed a heart rate of 87 beats/minute, regular with a QTc of 415

msec. The patient was instructed to attend the Patient Activity Center for some physical activity to help with anxiety. The patient was not noted to be panicked or requesting medication, and the taper of valbenazine was held.

On 3/6/2020 the internist was consulted by phone regarding the patient's asymptomatic intermittent tachycardia and QTc prolongation. It was recommended that the patient have an EKG in light of the patient's hemodynamic stability and no clinical symptoms.

On 3/9/2020 the internist evaluated the patient for tachycardia and noted that the EKG was abnormal with sinus tachycardia, rate 109 beats/min. The patient denied history of cardiac disease, chest pain, or palpitations. It was noted that the patient has an active order for atropine (sublingual) at bedtime as needed. The internist noted that clozapine can cause tachycardia and that the atropine may also inadvertently increase heart rate. An EKG was scheduled for 3/14/2020. A magnesium level on 3/10/2020 was 2.1 mEq/l.

On 4/1/2020, the attending changed the clozapine from 225mg oral daily at 7 PM and 75mg oral at noon to 100mg oral three times daily and increased the propranolol to 40mg oral twice daily. The attending documented considering benzodiazepines, reducing valbenazine to 40mg oral daily, and adding divalproex sodium or gabapentin.

On 4/20/2020 the attending noted that the patient has expressed anxiety. There was no evidence of tardive dyskinesia or dystonia. The plan was to continue clozapine, valbenazine 80mg oral daily, and propranolol 40mg oral twice daily.

The attending considered clozapine and atropine to be the reasons for the patient's tachycardia. The patient had been started on valbenazine for his tardive dyskinesia which resulted in improved awareness and social skills, and a decrease in tardive dyskinesia. The patient had demonstrated restlessness and fidgeting before starting valbenazine. Propranolol was started and titrated for anxiety and akathisia, which was more pronounced after valbenazine was started. No adverse events or serious side effects were observed/ reported with the valbenazine. The attending was uncertain whether the akathisia was a side effect of the valbenazine or a symptom that the patient had prior to valbenazine but was unable to verbalize until after treatment with valbenazine.

Medications:
Fish oil 1200mg oral daily 3/9/2020 to present
Pantoprazole 40mg oral daily 1/31/2020 to present
Atropine 1% Ophthalmic Solution 1 drop sublingual at bedtime as needed 6/28/2019 to 6/24/2020; changed to 1 drop sublingual at bedtime 7/6/2020 to present
Docusate sodium 100mg oral twice daily as needed 6/28/2019 to present
Multivitamin 1 tablet oral daily 3/9/2020 to present
Acetaminophen 650mg oral every 8 hours as needed 1/29/2020 to present

ADR: lithium, olanzapine/ EKG abnormalities

A 36-year-old Caucasian female was admitted to a state hospital with a diagnosis of schizoaffective disorder bipolar type. During her hospital stay she was treated with antipsychotics for the management of psychotic symptoms and mood stabilizers for mood symptoms. Her baseline labs and electrocardiogram (EKG) on admission were within normal limits. Subsequent labs and EKGs were generally normal. Nine months after hospitalization, lithium was initiated. Two weeks prior to initiating lithium, her EKG was normal with a QT interval corrected for heart rate (QTc) of 438msec and normal sinus rhythm. Two and half weeks after lithium initiation, a follow up EKG was obtained, and her EKG showed a QTc interval of 510msec. Another repeat EKG that day showed a QTc interval of 470msec, contour QRS abnormality, and tachycardia with a heart rate of 108 beats per minute (bpm). Another EKG was ordered the following day and QTc interval was prolonged at 479msec. Lithium was then reduced from 600mg twice daily to 450mg in the morning and 600mg at bedtime and olanzapine was reduced from 15mg at bedtime to 10mg at bedtime. A follow up EKG eight days later showed a reduction in the QTc interval to 459msec but still at a threshold where QTc prolonging agents should not be initiated. The patient was more irritable and her mood was unstable, as a result, her lithium dose was increased back to 600mg twice daily 13 days after the dose reduction and olanzapine was discontinued. Another EKG completed three days after lithium dose increase and olanzapine discontinuation showed a QTc interval of 356msec with incomplete right bundle branch block. Olanzapine 5mg daily was restarted three weeks after its discontinuation due to re-emergence of psychotic symptoms. Her EKG a month after the initial significant QTc prolongation was identified showed a QTc interval of 360msec with continued incomplete right bundle branch block. Olanzapine was increased to 10mg daily four days later. A repeat EKG one month later showed a QTc interval of 454msec, with continued incomplete right bundle branch block and a normal heart rate of 74 bpm. Her vital signs that day were within normal limits. Olanzapine was subsequently reduced to 7.5mg daily and soon after the patient was discharged

Medications administered within 24 hours of identified QTc prolongation: lactobacillus 1 cap twice daily, iron sulfate 325mg in the morning, metformin 500mg with morning meal, lithium 600mg twice daily, olanzapine 15mg at bedtime, omeprazole 20mg at 5 pm, loratadine 10mg at bedtime, melatonin 10mg at bedtime, propranolol 20mg twice daily, and Cepacol lozenge as needed.

The patient is on multiple agents implicated in QTc prolongation (Risperdal Consta, olanzapine, and lithium) which likely contributed to the significant increase in her QTc interval. Credible Meds lists lithium as one of the most likely agents to prolong QTc interval, with olanzapine and risperidone also being culprits. While this patient remained on lithium, her QTc normalized upon the initial dose reduction and continued to remain within normal limits even after the dose was increased back to 600mg twice daily. On lowered doses of olanzapine and lithium the QTc interval was within normal level. When the lithium dose increased and olanzapine discontinued,

the QTc interval also remained within normal limits. Upon re-initiation of olanzapine, the QTc interval remained normal initially but following increased olanzapine dose, QTc significantly increased. Right bundle branch block continues to be an anomaly on the EKG that was not noted prior to concomitant use of lithium and olanzapine and persisted with lithium monotherapy and upon reintroduction of olanzapine. It is difficult to confidently attribute causality to lithium alone, however it is likely the psychotropic polypharmacy served as a catalyst to the EKG changes noted in this patient.

ADR: trazodone, hydroxyzine/ priapism

A 37-year-old Hispanic male with schizoaffective disorder, depressive type and polysubstance abuse was admitted to a state hospital on 1/24/2020. He was continued on his pre-admission treatment regimen of haloperidol, divalproex ER, lithium ER, and fluoxetine. Minor lithium dosage adjustments were made in response to trough levels throughout the admission, trough levels ranged from 0.5 mmol/L to 0.92 mmol/L. Trazodone 100mg at bedtime as needed for insomnia was added on 2/10/2020, hydroxyzine 50mg twice daily as needed for anxiety or agitation was added on 2/14/2020, and melatonin 5mg at night was added on 2/25/2020. He received trazodone a total of nine times over the month the medication order was active and received hydroxyzine twice during that time frame. On 3/3/2020, he received trazodone at 0045 and then received hydroxyzine at 0310. On 3/7/2020, he received hydroxyzine and trazodone at 2310. Per the medication administration record, there were no other times when the patient received these two medications on the same day. Trazodone was discontinued on Monday 3/9/2020 at 9:25am with a discontinuation reason that there had been a reported episode of priapism which occurred over the previous weekend. The incident was not documented in the electronic medical record at the time of the occurrence and was not communicated to the on call provider or any provider until Monday. The incident occurred the evening of Saturday 3/7/2020; the erection reportedly lasted at least four hours ("all night" per patient) per the provider's note, later mentioned to possibly have been seven hours. On Monday, the provider was notified and the patient was interviewed. At that time, the patient denied any pain associated with the erection, and reported that he had had an erection since that episode. The provider has since educated the nursing staff that priapism is a medical emergency requiring notification of the on call provider. The order for trazodone was discontinued.

The trazodone package insert includes a warning of a risk of priapism (painful erections lasting 6+ hours). There are many published case reports of priapism with trazodone, but the incidence is still rare, listed as <1% on Lexi-Drugs. One published case report was found in a patient experiencing priapism with hydroxyzine, which was hypothesized to be related to structural similarities between hydroxyzine metabolite (norchlorcyclizine) and a trazodone metabolite (M-chlorophenyliperazine) (Neuropsychobiology. 1994;30(1):4-6.). This patient did receive a dose of hydroxyzine at the same time as his dose of trazodone the day of the prolonged

erection, and there was no other documented time that he received these medications together at the same time. It is possible that the combination of both trazodone and hydroxyzine contributed to this occurrence.

The other medications that this patient was receiving were all scheduled and were not new additions to his regimen, nor had the doses been recently adjusted. There are some case reports associated with lithium, but most involve lithium in combination with an atypical antipsychotic (J Neuropsychiatry Clin Neurosci. 2015 Winter;27(1):e77; Aust N Z J Psychiatry. 2004 May;38(5)381; J Clin Psychopharmacol. 1994 Dec;14(6):434-5), and this patient was not on a concomitant atypical antipsychotic. Priapism is listed as a possible adverse reaction in haloperidol and fluoxetine's package inserts, and Lexi-drugs lists the incidence of priapism <1%. However, published case reports were not found for haloperidol. There is at least one published case report of priapism associated with valproate sodium occurring five months after medication initiation and remitting after discontinuation (Indian J Pharmacol. 2013 Nov-dec;45(6):629-30.). There were no published case reports associated melatonin with priapism.

Although some of his other medications do have some small risk of priapism, the most likely cause of this adverse effect in this instance was a combination of trazodone and hydroxyzine.

Note: the committee discussed the importance of making sure that patients understand that priapism is a potentially serious side effect of trazodone treatment.

ADR: valproic acid/ hyperammonemia

A 36-year-old African American female with schizoaffective disorder bipolar type was admitted to a state hospital on 10/23/19. Her admission labs showed only minor abnormalities with high eosinophils 6.3% (reference range 1-3), low red blood cell count 4.14 M/mm3 (reference range 4.2-5.4), high red cell distribution width 15.3% (reference range 11.5-14.5), and high blood glucose 146 mg/dl (reference range 70-110). Hepatitis panel, HIV, and RPR were negative. AST/ALT were normal, and hemoglobin A1c was 5.5%. Upon admission, she was restarted on olanzapine oral dissolving tablet (ODT), which she had been on in jail, at 15mg twice daily. Early in her admission, she was labile and aggressive, requiring multiple holds and STAT meds (lorazepam 2mg by mouth STAT was given 20 times between admission and 12/28/19, she also received chlorpromazine 50mg by mouth six times between admission and 11/14/2019). Divalproex ER was added on 11/5/19 at a dose of 1000mg/day (11 mg/kg). The valproic acid level (VPA) level was 88.6 mcg/ml on 11/13/2019 at 2:05pm. Divalproex ER was then increased to 1500mg/day (17 mg/kg) on 12/5/2019. The VPA level was 76.5 mcg/ml on 12/10/2019 at 2:41pm. Chlorpromazine was added on 11/14/2019 and titrated up by 50mg twice daily every 1-2 weeks to a dose of 250mg twice daily on 12/19/2019. On 12/28/2019, she received STAT lorazepam 2mg by mouth at 2:18am. Later that morning, at 10:29am, she was described as "sleepy" by nursing staff, and the on-call provider was paged.

Nursing documentation indicates she was sleeping in the day room and occasionally calling out. She was noted to have deep and even respirations and good color. Staff helped her to her room via wheelchair. She was able to lift her legs while moving but was lethargic and mumbling, and was not opening her eyes. Her morning medications (including chlorpromazine and olanzapine) had been held due to reports of lethargy and she had not eaten breakfast. As of 11:15am, she was still asleep, and her vital signs were oxygen saturation 99%, blood pressure 137/93, heart rate of 89 bpm, and a documented respiratory rate (RR) of 10 breaths per minute (it is possible this was a typo in the nursing note, as the note indicates her breathing was deep, even, and not labored and documentation indicates normal RR about 45 minutes later). She was assisted to a sitting position, where she sat assisted for two minutes, but then wanted to lay down. Vital signs at 12:30pm were oxygen saturation 99%, RR 18 breaths per minute, heart rate 100 bpm, BP 151/99, temperature 96.5°F, and normal blood glucose of 123mg/dl. Per the providers note, the patient was sedated/obtunded, minimally responsive, had equal and responsive pupils, evenly rigid on exam but no noted hyper reflexia or myoclonus, and she has not exhibited any fever, sweating, or autonomic instability. Antipsychotics were held. The provider documented some concern for neuroleptic malignant syndrome (NMS). The provider consulted with another provider that had seen the patient during what was thought to be a similar presentation the night before and determined that the patient's presentation had worsened, as she had become less responsive and more lethargic. She was transferred to a medical hospital for workup. Upon transfer, it was noted that the she had an elevated ammonia level of 118 umol/L (reference range 16-53). It was felt that this was related to divalproex use, so this medication was discontinued. The patient was also treated with lactulose. A liver ultrasound was consistent with fatty infiltration or other hepatic parenchymal disease, and records indicate that a 2015 computerized tomography (CT) scan also suggested fatty liver. The patient reportedly responded well to lactulose and returned to the state hospital two days later on 12/30/2019. Her ammonia level was improved to 55 umol/L on 12/31/2019; at that time, her presentation was documented to be at baseline. Lactulose was continued and divalproex was not restarted. Follow up ammonia levels were not checked.

Hyperammonemia and related encephalopathy is a well-documented adverse effect of divalproex and is listed as a warning in the package insert. There are also many published case reports detailing patients who developed VPA induced hyperammonemia encephalopathy. According to one retrospective study of 357 patients who received valproic acid and had their ammonia checked at least once, 36% of the patients had hyperammonemia. Of those patients with high ammonia levels, 43.2% were symptomatic (symptoms included lethargy, altered mental status, confusion, stupor, delirium, disorientation, vomiting, seizure) (Ment Health Clin 2018 Mar; 8(2):73-77). This suggests that many patients have elevated ammonia with no associated symptoms. The exact mechanism is unknown, but it is thought to be related to impairing the urea cycle through various pathways

(increased renal uptake of glutamine, depletion of hepatic carnitine and N-acetyl glutamate, and increased accumulation of glutamine in astrocytes) (J Hepatol. 2011 Aug; 55(2):426-434).

This patient had not had any major medication changes in at least 10 days prior to the instance of altered mental status, but she did receive an oral dose of lorazepam 2mg about 8 hours prior to the physician being paged. She had received a similar dose of lorazepam 20 times during her admission at that point, although these doses had been given either prior to scheduled chlorpromazine being initiated or when chlorpromazine was at a lower scheduled dose (the highest dose she had been taking when given previous doses of STAT lorazepam 2mg was 150mg twice daily). Otherwise most medications were similar. This patient also had some indication of liver damage, with CT's suggesting fatty liver. The hyperammonemia was likely caused by a combination of liver damage and valproic acid use.

New Drug Applications

Conflict of Interest disclosure forms were previously received from the non-committee members who had submitted the new drug application and/or prepared the monograph. No new conflicts were disclosed.

Eszopiclone (Lunesta®)

Presented by Dr. Hall. Please refer to Appendix A for the monograph that was considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of eszopiclone to the formulary in the Miscellaneous Anxiolytics and Hypnotics section.

The formulary check list was completed and no issues were detected.

Sitagliptin (Januvia®)

Presented by Dr. Mican. Please refer to Appendix B for the monograph that was considered when determining action by the committee.

The committee elected to table a decision on adding sitagliptin to the formulary at this time. Dr. Hall will present a review of Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors at the next meeting.

Hepatitis C Drug Purchases

For the third quarter of fiscal year 2020 (March 2020 to May 2020), the following purchases for drugs to treat hepatitis C were made:
State Hospitals: $0
State Supported Living Centers: $0

Quarterly Non-Formulary Drug Justification Report

For the third quarter of fiscal year 2020 (March 2020 to May 2020), only the state hospitals reported use of non-formulary agents. The state supported living centers

(SSLCs) currently do not have the capability to obtain non-formulary drug usage reports from their computer system but are working with the vendor to make this reporting possible. The following were the top five non-formulary agents, by number of orders, that were prescribed in the state hospitals during the third quarter of fiscal year 2020:

- Quercetin (plant flavonoid dietary supplement)
- Acetaminophen-caffeine- pyrilamine (Midol Menstrual Complete®)
- Flaxseed oil
- Sitagliptin (Januvia®)
- Brivaracetam (Briviact®)

Drug Formulary Sectional Review

In reviewing the formulary drug listings for antiparkinson agents and cardiovascular agents, the committee approved the following changes:

- Antiparkinson Agents
  - No changes at this time.
- Cardiovascular Agents
  - Remove triamterene, felodipine, fluvastatin, and gemfibrozil from the formulary.
  - Remove "Prior failure to ACE inhibitor therapy due to intolerable side effects" from Reserve Drug Guidelines for Use for olmesartan.

ISMP Targeted Medication Safety Best Practices for Hospitals 2020-2021

The committee reviewed the ISMP document, with particular focus on best practice 13- Eliminate injectable (IV and IM) promethazine from the formulary. The committee will review a monograph for injectable ondansetron and discuss removing promethazine from the formulary at the next meeting.

Other Formulary Changes

At the previous PEFC meeting, the committee recommended the removal of zaleplon from the formulary due to lack of use. The committee did not receive any feedback from the field regarding this deletion and the formulary has been updated.

Resource Links Review

The committee approved a recommendation to add a link to the Beers Criteria list to the resource links document.

The updated document will be posted to the PEFC website.

Psychotropic Audit Checklist & Guidelines Review

The committee reviewed and approved revisions to the following audit criteria:

- benzodiazepines

- gabapentin
- buspirone
- sedating antihistamines
- non-benzodiazepine sedative/hypnotics

The checklists will be updated to include indications, absolute contraindications, and monitoring parameters from the revised guideline documents (these three items were chosen to be the basic components of a medication use audit at the April 2019 committee meeting). The updated documents will be posted to the PEFC website.

Psychotropic Inpatient Monitoring Guidelines Table Review

The committee reviewed and approved recommended revisions to the Psychotropic Inpatient Monitoring guidelines table. The updated document will be posted to the PEFC website.

Psychotropic Audit Checklist & Guidelines Review Schedule

The committee reviewed the revised schedule for January 2021 to July 2023 reviews.

Issues from the Chief Medical Officer, State Hospitals

Dr. Muse will be retiring from her position as Chief Medical Officer for the state hospitals. Dr. Beadles will be taking on the position in the interim until a new chief is announced.

Issues from the Medical Services Coordinator, SSLCs

Dr. Shipley was not present to provide a report.

Drug Shortages, Recalls, and FDA Safety Communications

The FDA has issued the following safety communications and recalls that may impact our facilities:

Shortages

Lithium oral solution: unavailable due to the shortage of the active pharmaceutical ingredient (API).
Sertraline: some product lines unavailable due to increased demand and shortage of API, other lines available on allocation.
Lorazepam: some product lines unavailable or on allocation due to increased demand.
Loxapine: most product lines unavailable or on allocation, several product lines have been discontinued.
Amoxapine: All Teva products are on backorder due to manufacturing delays caused by capacity constraint.

Recalls

Metformin extended release tablets: Testing by the FDA which showed N-Nitrosodimethylamine (NDMA) concentrations in excess of the Acceptable Daily Intake Limit (ADI) resulted in the following recalls:

- Apotex: all lots of 500 mg
- Amneal: all lots of 500 mg and 750 mg
- Teva: 14 lots of 500 mg and 750 mg; all ER forms have now been discontinued.
- Marksans Pharma: one lot of 500 mg
- Lupin Pharmaceuticals: all lots of 500 mg and 1000 mg
- Granules Pharmaceuticals: 12 lots of 750 mg

Safety-related Labeling Changes

Fluoxetine: Use in Specific Populations: (additions and/or revisions are in italics)
Pregnancy—Advise pregnant women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with PROZAC. Advise patients that fluoxetine use later in pregnancy may lead to increased risk f*or neonatal complications requiring prolonged hospitalization, respiratory support, tube feeding, and/or persistent pulmonary hypertension of the newborn (PPHN).*
Advise women that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to fluoxetine during pregnancy.
Lactation—Advise breastfeeding women using fluoxetine to monitor infants for agitation, irritability, poor feeding and poor weight gain and to seek medical care if they notice these signs.

Pradaxa: **Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome** *(Newly added section)*
Direct-acting oral anticoagulants (DOACs), including PRADAXA, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple-positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Open Forum

No items.

Next Meeting Date

The next meeting is scheduled for October 30, 2020.

Adjourn

There being no further business, the meeting was adjourned at 3:04 p.m.

Approved: *David Moron*

David Moron, MD, Interim Chairman

Minutes Prepared by:

Jean Baemayr, PharmD

Appendix

- Appendix A – eszopiclone (Lunesta®) monograph
- Appendix B – sitagliptin (Januvia®) monograph

Appendix A

Eszopiclone (Lunesta®)

Classification:

Hypnotic

Pharmacology

The mechanism of action of eszopiclone (Lunesta) as a hypnotic is unclear; however, its effect could be related to its interaction with GABA-receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors.

Indication -FDA & literature supported non-FDA

Treatment of insomnia (decreased sleep latency and improved sleep maintenance)

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Rapidly absorbed. Peak plasma concentrations achieved within approximately 1 hour after oral administration
Distribution	Weakly bound to plasma protein (52-59%)
Metabolism	Hepatic via oxidation and demethylation (CYP2E1, 3A4); (S)-N-desmethylzopiclone metabolite has less activity than parent compound
Excretion	Urine (up to 75%, primarily as metabolites; < 10% as parent drug)

Z-drug	T-max (h)	Oral bioavailability	Elimination t ½ (h)	Dose range	Metabolism
Zolpidem IR	1-2	65-70%	2.5-3	5-10 mg	CYP 3A4, 2C9, 1A2
Zolpidem ER	1.5-2.5	65-70%	2.5-3	6.25-12.5 mg	
Zopiclone	1.5-2	75-80%	5-6	3.75-7.5	CYP 3A4, 2C8

Z-drug	T-max (h)	Oral bioavailability	Elimination t ½ (h)	Dose range	Metabolism
Eszopiclone	1-1.5	75-80%	6-7	1-3 mg	CYP 3A4, 2E1
Zaleplon	0.7-1.4	30%	1	5-20 mg	Aldehyde oxidase, CYP 3A4

Dosage/Administration

The recommended starting dose in adults is 1 mg, once daily immediately before bedtime. Dosing can be raised to 2 mg or 3 mg if clinically indicated.

The total dose should not exceed 2 mg in **elderly or debilitated patients**.

No dose adjustment is necessary for patients with **mild-to-moderate hepatic impairment**. In patients with severe hepatic impairment, the total dose of eszopiclone should not exceed 2 mg.

In patients coadministered eszopiclone with **potent CYP3A4 inhibitors,** the total dose of eszopiclone should not exceed 2 mg.

Taking eszopiclone (Lunesta) with or immediately after a heavy, high-fat meal results in slower absorption and would be expected to reduce the effect of eszopiclone (Lunesta) on sleep latency.

Use in Special Population

Available pharmacovigilance data with eszopiclone (Lunesta) use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies conducted in pregnant rats and rabbits throughout organogenesis, there was no evidence of teratogenicity. Administration of eszopiclone to rats throughout pregnancy and lactation resulted in offspring toxicities at all doses tested; the lowest dose was approximately 200 times the maximum recommended human dose (MRHD) of 3 mg/day based on mg/m2 surface area. The offspring toxicities included reduced fetal weight, increased skeletal variations, increased post-implantation loss, decreased postnatal pup weights and survival, and increased pup startle response.

There are no data on the presence of eszopiclone in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for eszopiclone and any potential adverse effects on the breastfed infant from eszopiclone or from the underlying maternal condition.

Safety and effectiveness of eszopiclone (Lunesta) have not been established in pediatric patients. Eszopiclone (Lunesta) failed to demonstrate efficacy in controlled

clinical studies of pediatric patients with Attention-Deficit/Hyperactivity (ADHD) associated insomnia.

The total dose should not exceed 2 mg in elderly or debilitated patients.

No dose adjustment is necessary for patients with mild-to-moderate hepatic impairment. In patients with severe hepatic impairment, the total dose of eszopiclone should not exceed 2 mg.

In patients coadministered eszopiclone with potent CYP3A4 inhibitors, the total dose of eszopiclone should not exceed 2 mg.

Caution is advised if eszopiclone (Lunesta) is prescribed to patients with compromised respiratory function.

No dose adjustment appears necessary in subjects with any degree of renal impairment, since less than 10% of eszopiclone (Lunesta) is excreted unchanged in the urine.

In primarily depressed patients treated with sedative-hypnotics, worsening of depression, including suicidal thoughts and actions (including completed suicides), have been reported in association with the use of sedative/hypnotics. Sedative-hypnotic drugs should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Contraindication

Complex sleep behaviors after taking eszopiclone (Lunesta)

Known hypersensitivity to eszopiclone (Lunesta)

Precautions

Boxed Warning: Complex sleep behaviors

Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur following the first or any subsequent use of eszopiclone (Lunesta). Patients can be seriously injured or injure others during complex sleep behaviors. Such injuries may result in a fatal outcome. Other complex sleep behaviors (e.g., preparing and eating food, making phone calls, or having sex) have also been reported. Patients usually do not remember these events. Post-marketing reports have shown that complex sleep behaviors may occur with eszopiclone (Lunesta) alone at recommended dosages, with or without the concomitant use of alcohol or other CNS depressants. Discontinue eszopiclone (Lunesta) immediately if a patient experiences a complex sleep behavior.

CNS Depressant Effects and Next-Day Impairment

Eszopiclone (Lunesta) is a CNS depressant and can impair daytime function in some patients at the higher doses (2 mg or 3 mg), even when used as prescribed. Prescribers should monitor for excess depressant effects, but impairment can occur in the absence of symptoms (or even with subjective improvement), and impairment may not be reliably detected by ordinary clinical exam (i.e., less than formal psychomotor testing). **While pharmacodynamic tolerance or adaptation to some adverse depressant effects of eszopiclone (Lunesta) may develop, patients using 3 mg eszopiclone (Lunesta) should be cautioned against driving or engaging in other hazardous activities or activities requiring complete mental alertness the day after use.**

Additive effects occur with concomitant use of other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol), including daytime use. Downward dose adjustment of eszopiclone (Lunesta) and concomitant CNS depressants should be considered.

The use of eszopiclone (Lunesta) with other sedative-hypnotics at bedtime or the middle of the night is not recommended.

The risk of next-day psychomotor impairment is increased if eszopiclone (Lunesta) is taken with less than a full night of sleep remaining (7- to 8 hours); if higher than the recommended dose is taken; if coadministered with other CNS depressants; or coadministered with other drugs that increase the blood levels of eszopiclone.

Because eszopiclone (Lunesta) can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls.

Need to Evaluate for Comorbid Diagnoses

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. *The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.* Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including eszopiclone (Lunesta). Because some of the important adverse effects of eszopiclone (Lunesta) appear to be dose related, it is important to use the lowest possible effective dose, especially in the elderly.

Severe Anaphylactic and Anaphylactoid Reactions

Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including eszopiclone (Lunesta). Some patients have had additional symptoms such as dyspnea, throat closing, or nausea and vomiting that suggest anaphylaxis. Some

patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with eszopiclone (Lunesta) should not be rechallenged with the drug.

Abnormal Thinking and Behavioral Changes

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g. aggressiveness and extroversion that seem out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Withdrawal Effects

Following rapid dose decrease or abrupt discontinuation of the use of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs.

Timing of Drug Administration

Eszopiclone (Lunesta) should be taken immediately before bedtime. Taking a sedative/hypnotic while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness.

Adverse Effects

Incidence of Adverse Reactions Observed at an Incidence of $\geq$ 2% in Controlled Trials (non-elderly adults, treatment duration = 6 weeks, n = 308 [placebo = 99, 2 mg = 104, 3 mg = 105]). Adverse reactions that suggest a dose-response relationship are in **bold type**

Headache—placebo = 13%, 2 mg = 21%, 3 mg = 17%
Dry Mouth—placebo = 3%, 2 mg = 5%, 3 mg = 7%
Dyspepsia—placebo = 4%, 2 mg = 4%, 3 mg = 5%
Nausea—placebo = 4%, 2 mg = 5%, 3 mg = 4%
Vomiting—placebo = 1%, 2 mg = 3%, 3 mg = 0%
Anxiety—placebo = 0%, 2 mg = 3%, 3 mg = 1%
Confusion—placebo = 0%, 2 mg = 0%, 3 mg = 3%
Depression—placebo = 0%, 2 mg = 4%, 3 mg = 1%
Dizziness—placebo = 4%, 2 mg = 5%, 3 mg = 7%

Hallucinations—placebo = 0%, 2 mg = 1%, 3 mg = 3%
Nervousness—placebo = 3%, 2 mg = 5%, 3 mg = 0%
Somnolence—placebo = 3%, 2 mg = 10%, 3 mg = 8%
Infection—placebo = 3%, 2 mg = 5%, 3 mg = 10%
Rash—placebo = 1%, 2 mg = 3%, 3 mg = 4%
Unpleasant Taste—placebo = 3%, 2 mg = 17%, 3 mg = 34%

Interactions

CNS Active Drugs

Dosage adjustments may be necessary when eszopiclone (Lunesta) is combined with other CNS depressant drugs because of the potentially additive effects

Drugs that Inhibit or Induce CYP3A4

CYP3A4 is a major metabolic pathway for elimination of eszopiclone (Lunesta). The exposure of eszopiclone (Lunesta) was increased by coadministration of ketoconazole, a potent inhibitor of CYP3A4. Other strong inhibitors of CYP3A4 (itraconazole, clarithromycin, nefazodone, troleandomycin, ritonavir, nelfinavir) would be expected to behave similarly. Dose reduction of eszopiclone (Lunesta) is needed for patient co-administered eszopiclone (Lunesta) with potent CYP3A4 inhibitors.

Drugs that Induce CYP3A4 (Rifampicin)

Racemic zopiclone exposure was decreased 80% by concomitant use of rifampicin, a potent inducer of CYP3A4. A similar effect would be expected with eszopiclone (Lunesta). Combination use with CYP3A4 inducer may decrease the exposure and effects of eszopiclone (Lunesta).

Efficacy

Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline

A task force commissioned by the AASM conducted a systematic review of evidence for individual agents commonly used to treat insomnia. Investigators assessed evidence using The GRADE process. The following were identified as critical outcomes: total sleep time (TST), sleep latency (SL), wake after sleep onset (WASO), and quality of sleep (QOS). The committee developed recommendations based on the quality of evidence, the balance of benefits and harms, and patient values and preferences. Below are the recommendations and a summary of critical outcomes for the benzodiazepine receptor agonists (BzRA).

Eszopiclone (based on trials of 2 mg and 3 mg doses)

- Recommendation: We suggest that clinicians use eszopiclone as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults.
- Direction and Strength of Recommendation: Weak

- Quality of evidence: Very low
- Benefits and Harms Assessment: Benefits outweigh harms
- Patients' Values and Preferences Assessment: The majority of patients would use this treatment (over no treatment), but many would not.
- Sleep latency: Mean reduction was 14 min greater, compared to placebo (95% CI: 3 to 24 min reduction)
- **Quality of sleep (subjective reporting): Moderate to Large improvement in quality of sleep, compared to placebo**
- **Total sleep time: Mean improvement was 28-57 min longer, compared to placebo (95% CI: 18 to 76 min improvement)**
- Wake after sleep onset: Mean reduction was 10-14 min greater, compared to placebo (95% CI: 2 to 18 min reduction)

Zaleplon (based on 10 mg doses)

- Recommendation: We suggest that clinicians use zaleplon as a treatment for sleep onset insomnia (versus no treatment) in adults
- Direction and Strength of Recommendation: Weak
- Quality of evidence: Low
- Benefits and Harms Assessment: Benefits outweigh harms
- Patients' Values and Preferences Assessment: The majority of patients would use this treatment (over no treatment), but many would not.
- Sleep Latency: Mean reduction was 10 min greater, compared to placebo (95% CI: 0 to 19 min reduction)
- Quality of Sleep (subjective reporting): No improvement compared to placebo

Zolpidem (based on trials of 10 mg doses)

- Recommendation: We suggest that clinicians use zolpidem as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults
- Direction and Strength of Recommendation: Weak
- Quality of Evidence: Very low
- Benefits and Harms Assessment: Benefits outweigh harms
- Patients' Values and Preferences Assessment: The majority of patients would use this treatment (over no treatment), but many would not.
- Sleep Latency: Mean reduction was 5-12 min greater, compared to placebo (95% CI: 0 to 19 min reduction)
- Quality of Sleep (subjective reporting): Moderate improvement in quality of sleep, compared to placebo
- Total Sleep Time: Mean improvement was 29 min longer, compared to placebo (95% CI: 11 to 47 min improvement)
- Wake after sleep onset: Mean reduction was 25 min greater, compared to placebo (95% CI: 18 to 33 min reduction)

Erman Study

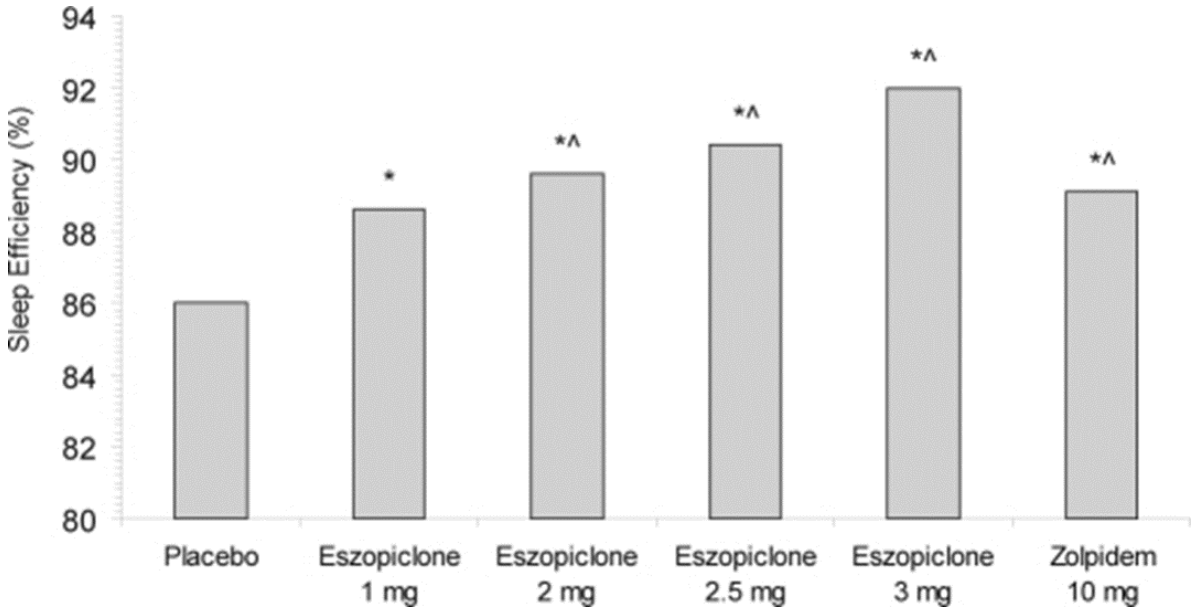
In a multicenter, randomized, blinded, 6-way crossover study, **Erman and colleagues** evaluated the polysomnographic efficacy and safety of a range of doses of eszopiclone (1 mg, 2 mg, 2.5 mg, 3 mg) compared to placebo in patients with primary chronic insomnia. Zolpidem 10 mg was included as an active control (but the study was not powered to test drug-drug differences).

Investigators enrolled 65 patients with primary chronic insomnia (DSM-IV) ranging in age from 21-64 years (mean = 40.6 y). Females outnumbered males approximately 3:1. Eligible patients reported a sleep duration of $\leq$ 6.5 h and time to fall asleep > 30 minutes each night for at least one month. Exclusion criteria included any clinically significant and/or unstable medical condition or chronic disease; DSM-IV Axis I or Axis II psychiatric illness or personality disorder; sleep apnea or restless legs syndrome/periodic leg movements disorder; history of substance abuse/dependence; use of any psychotropic, hypnotic, or other medications (including herbal supplements or melatonin) that affect sleep; or use of other prescription or over-the-counter medications (including those that contain caffeine, diphenhydramine, or ephedrine) that affect sleep or whose use is contraindicated with hypnotics.

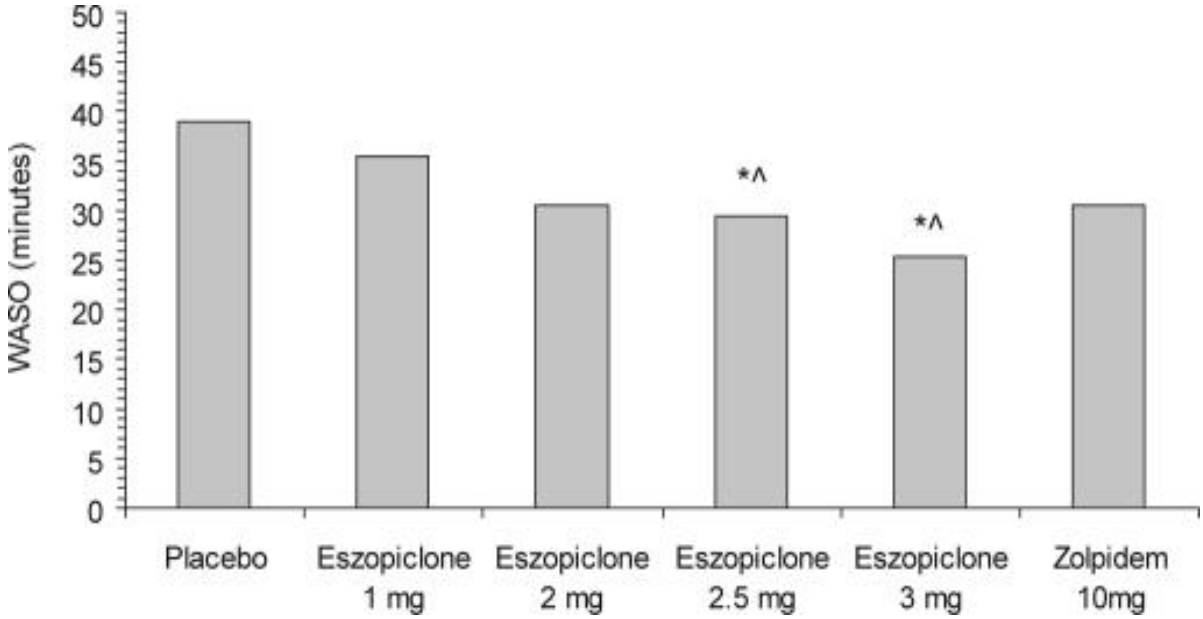
Each patient received all six treatments in random order; a three- to seven-day washout period separated each treatment. For each treatment, polysomnography (PSG) was performed on two consecutive nights. The primary endpoint was latency to persistent sleep (LPS), which was defined as time from the onset of PSG recording to the beginning of 10 continuous minutes of sleep. Secondary endpoints included sleep efficiency (SE) and wake time after sleep onset (WASO). Sleep efficiency is total sleep time (minutes) divided by total recording time (minutes) multiplied by 100. Wake time after sleep onset (WASO) is the number of minutes of wakefulness (after the onset of persistent sleep) to the end of the PSG recording.

Patients completed morning questionnaires to report subjective sleep latency (sSL), subjective total sleep time (sTST), sWASO, sleep quality (0-100 point Visual Analog Scale) and depth of sleep (0-100 point Visual Analog Scale), and morning sleepiness (0-100 point Visual Analog Scale). Patients completed evening questionnaires to report ability to function and daytime alertness (0-100 point VAS). Laboratory evaluations, physical and neurological examinations, ECGs, and vital signs were obtained at screening and the end of study visit (5 to 7 days after the last dose of study medication). Patients reported adverse events throughout the trial.

Relative to placebo, all active treatments significantly reduced ($p < 0.05$) median LPS by 42% to 55%. Median LPS were as follows: 13.1 minutes for eszopiclone 3 mg; 13.1 minutes for zolpidem 10 mg; 13.8 minutes for eszopiclone 2.5 mg; 15.5 minutes for eszopiclone 2 mg; 16.8 minutes for eszopiclone 1 mg; 29.0 minutes for placebo. Relative to placebo, all active treatments significantly increased ($p < 0.05$) SE.



Relative to placebo, eszopiclone 3 mg and eszopiclone 2.5 mg significantly decreased median WASO. None of the other treatment arms demonstrated a significant difference versus placebo.



In general, treatment with eszopiclone 2 mg, eszopiclone 3 mg, and zolpidem 10 mg resulted in improved patient-reported measures of sleep compared to treatment with placebo. These measures included sSL, sTST, quality of sleep, depth of sleep, and daily ability to function (VAS). Median sSL for eszopiclone 2 mg, eszopiclone 3 mg, zolpidem 10 mg, and placebo were 25.0 min, 25.0 min, 25.0 min, and 47.5 min, respectively (all $p < 0.05$ vs placebo). Median sTST for eszopiclone 2 mg, eszopiclone 3 mg, zolpidem 10 mg, and placebo were 412.5 min, 420.0 min, 411.3 min, and 375.0 min, respectively (all $p < 0.05$ vs placebo). Median quality of sleep (VAS) for eszopiclone 2 mg, eszopiclone 3 mg, zolpidem 10 mg, and placebo were 58.0, 62.0, 56.0, 43.5, respectively (all $p < 0.05$ vs placebo). Median depth of sleep

(VAS) for eszopiclone 2 mg, eszopiclone 3 mg, zolpidem 10 mg, and placebo were 56.5, 59.5, 56.5, 40.3, respectively (all $p < 0.05$ vs placebo). Median daily ability to function for eszopiclone 2 mg, eszopiclone 3 mg, zolpidem 10 mg, and placebo were 59.0, 60.0, 53.0, 50.0, respectively (all $p < 0.05$ vs placebo).

Summary of Adverse Events

There were no clinically relevant changes in blood profiles, ECGs, physical findings, or vital signs.

Adverse event*	Placebo (n = 63)	Eszopiclone 1 mg (n = 63)	Eszopiclone 2 mg (n = 63)	Eszopiclone 2.5 mg (n = 65)	Eszopiclone 3 mg (n = 64)	Zolpidem 10 mg (n = 64)	Overall p-value
All adverse events	25.4%	19.0%	25.4%	35.4%	32.8%	32.8%	0.300
All CNS adverse events	7.9%	7.9%	6.3%	6.2%	12.5%	23.4%	0.012
Dizziness	4.8%	3.2%	0	0	4.7%	10.9%	0.017
Headache	9.5%	4.8%	6.3%	3.1%	9.4%	9.4%	0.590
Somnolence	3.2%	4.8%	3.2%	3.1%	4.7%	9.4%	0.530
Hallucinations	0	0	0	0	0	4.7%	0.010
Unpleasant taste	1.6%	4.8%	4.8%	9.2%	7.8%	0	0.120
Nausea	3.2%	3.2%	1.6%	3.1%	3.1%	6.3%	0.810

*Includes adverse events that were reported by ≥ 4% of patients in any treatment group.

Dosage Forms

Eszopiclone (Lunesta) is available in 1 mg, 2 mg, and 3 mg strengths for oral administration.

Summary/Conclusion

Cognitive behavioral therapy for insomnia (CBT-I) and pharmacotherapy are two primary methods of treating insomnia. The AASM Clinical Practice Guideline for Chronic Insomnia recommends the following pharmacotherapeutic agents for sleep onset insomnia: eszopiclone (Lunesta), ramelteon (Rozerem), **temazepam (Restoril)**, **triazolam (Halcion),** zaleplon (Sonata), and **zolpidem (Ambien)**. Recommendations for sleep maintenance insomnia include **doxepin** (Silenor), eszopiclone (Lunesta), **temazepam (Restoril),** suvorexant (Belsomra), and **zolpidem (Ambien)**.

While the only benzodiazepine receptor agonist currently on formulary is zolpidem (Ambien), eszopiclone (Lunesta) is widely used throughout the Texas HHSC system. Based on the AASM Clinical Practice Guideline for Chronic Insomnia, eszopiclone

(Lunesta) may offer some advantages over zolpidem for quality of sleep (moderate to large improvement vs moderate improvement) and total sleep time compared to placebo (28-57 min longer vs 29 min longer). In the Erman study, approximately twice as many patients reported CNS adverse events (dizziness, somnolence, hallucinations) with zolpidem 10 mg compared to eszopiclone 3 mg. The authors theorized that this could be secondary to differences in relative peak plasma concentrations between the two agents and/or different benzodiazepine receptor binding profiles which lead to varied allosteric modulation of GABA activity.

Recommendation

Eszopiclone (Lunesta) should be added to the formulary.

References

1. Erman MK, Zammit G, Rubens R, et al. A Polysomnographic Placebo-Controlled Evaluation of the Efficacy and Safety of Eszopiclone Relative to Placebo and Zolpidem in the Treatment of Primary Insomnia. Journal of Clinical Sleep Medicine 2008;4(3):229-234.
2. Gunja N. The Clinical and Forensic Toxicology of Z-drugs. J Med. Toxicol. (2013) 9: 155-162.
3. Lunesta (eszopiclone) [package insert]. Marlborough (MA): Sunovion Pharmaceuticals Inc.; 2019.
4. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2017;13(2):307-349.

Prepared by:
Catherine Hall, PharmD, BCPP, BCACP
Clinical Pharmacist
San Antonio State Hospital
August 2020

Appendix B

Sitagliptin (Januvia®)

Classification:
Antidiabetic Agent

Pharmacology
JANUVIA® (sitagliptin) is a dipeptidyl peptidase-4 (DPP-4) inhibitor which slows the inactivation of endogenous incretin hormones. Incretin hormones including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. Sitagliptin exerts its action by inhibiting the enzyme DPP-4 and this activity lasts for a 24-hour period.

Indication- FDA Approved
Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	The absolute bioavailability is approximately 87%. Oral administration of sitagliptin 100 mg is rapidly absorbed with a peak plasma concentration (T_{max}) occurring 1 to 4 hours postdose.
Distribution	38% reversibly bound to plasma proteins. The V_d of 100 mg IV sitagliptin is 198 L.
Metabolism	Approximately 16% of an oral dose is excreted as metabolites. Six metabolites were detected at trace levels and not expected to contribute to the activity of sitagliptin. The primary enzyme responsible for metabolism is CYP3A4 with contribution from CYP2C8.
Excretion	79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. The terminal $t_{1/2}$ following a 100 mg oral dose is approximately 12.4 hours and renal clearance is 350 mL/min.

Dosage/Administration

JANUVIA® (sitagliptin) is recommended at a dose of 100 mg once daily with or without food.

Dose adjustment is needed for moderate to severe renal impairment:

- eGFR 30 to 45 ml/min 50 mg once daily
- eGFR < 30 ml/min including end stage renal disease on dialysis 25 mg once daily

Use in Special Populations

Pregnancy

Limited data available in pregnant women and not sufficient to inform a drug-associated risk for major birth defects and miscarriage. There are risks to mother and fetus associated with poorly controlled diabetes in pregnancy. No adverse developmental effects were observed when sitagliptin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 30-times and 20-times the clinical dose based on AUC. Healthcare providers are encouraged to report any prenatal exposure to sitagliptin by calling the pregnancy registry at 1-800-986-8999.

Lactation

There is no information regarding the presence of sitagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. Sitagliptin is present in rat milk and therefore possibly present in human milk. Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1.

Pediatric Use

Safety and effectiveness of JANUVIA® (sitagliptin) in pediatric patients below the age of 18 years have not been established.

Geriatric Use

Studies utilizing JANUVIA® (sitagliptin) in patients 65 years and older in pre-approval clinical safety and efficacy studies were limited and consisted of 725 of the 3884 subjects (19%). Patients 75 years and older consisted of 61 of the 3884 subjects (1.6%). Available evidence has not identified differences in response between elderly and younger patients, although greater sensitivity in some older individuals cannot be ruled out. Since sitagliptin is primarily renally eliminated and aging may be associated with reduced renal function, renal function should be evaluated more frequently in elderly patients to see if dose adjustment may be necessary.

Renal Impairment

Sitagliptin is primarily excreted by the kidneys and exposure is increased in those with renal impairment. Lower doses are recommended in those with moderate to severe renal impairment (eGFR < 45ml/min).

Contraindications

History of serious hypersensitivity reaction to sitagliptin such as anaphylaxis or angioedema.

Precautions

- Pancreatitis: Postmarketing reports of hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue.
- Heart failure: Heart failure has been reported with two other members of the DPP-4 inhibitor class. Consider risk vs. benefit for those with risk factors for heart failure and monitor patients for signs and symptoms.
- Acute Renal Failure: Postmarketing reports of acute renal failure. Assess renal function prior to initiation and periodically thereafter.
- Increased risk of Hypoglycemia when sitagliptin added to insulin secretagogue (e.g. sulfonylurea) or insulin therapy. Consider lowering dose if sitagliptin is added to these therapies.
- Hypersensitivity reactions have been reported in postmarketing reports including anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome.
- Arthralgia and severe joint pain reported in patients taking DPP-4 inhibitors.
- Bullous pemphigoid noted in postmarketing reports. Tell patients to report the development of blisters or erosions.

Adverse Effects

Adverse reactions occurring in 5% or more of JANUVIA® (sitagliptin) treated patients and at a rate greater than placebo are:

- Upper respiratory tract infection 6.3%
- Nasopharyngitis 5.2%
- Headache 5.1%

Other notable adverse effects reported:

- Incidence of acute pancreatitis was 0.1 per 100 patient years in each group (4 patients in the sitagliptin group and 4 in the control group)
- Incidence of hypoglycemia in the monotherapy trials was 1.2% sitagliptin and 0.9% placebo group
- In a 12-week study the mean increase in Scr was 0.12 mg/dL for sitagliptin and 0.07 mg/dL for placebo, the clinical significance of this increase relative to placebo is not known
- No meaningful changes in vital signs or ECG including QTc interval were observed

Monitoring

- A1C quarterly for those not meeting glycemic goals (ADA goal <7% is recommended for most nonpregnant adults)
- A1C at least twice yearly for those meeting glycemic goals

- Monitor renal function baseline and periodically thereafter
- Monitor for hypoglycemia, particularly if added to insulin secretagogue (e.g. sulfonylurea) or insulin therapy
- Monitor for any signs or symptoms of new or worsening heart failure
- Hypersensitivity reactions and bullous pemphigoid including blisters or erosions

Interactions

Digoxin

Slight increase in AUC (11%), no dosage adjustment recommended

Insulin Secretagogues or Insulin

Coadministration may require lower dose to reduce risk of hypoglycemia. Rate of hypoglycemia (glucose < 70 mg/dL) 12.2% with sitagliptin 100 mg + glimepiride vs. 1.8% with glimepiride alone. Rate of severe hypoglycemia 0% for both. Rate of hypoglycemia 15.5% with sitagliptin 100 mg + insulin vs. 7.8% with insulin alone. Rate of severe hypoglycemia 0.6% for sitagliptin 100 mg + insulin vs. 0.3% for insulin alone. Severe hypoglycemia was defined as incidents requiring medical assistance, exhibiting depressed level/loss of consciousness or seizure.

Efficacy

Monotherapy Studies

Two monotherapy pre-approval studies were conducted in patients with type 2 diabetes, one 18 weeks in duration and the other 24 weeks in duration. Those entering the study currently on an antihyperglycemic agent underwent a 7-week washout period. Those with inadequate glycemic control (A1C 7% to 10%) after the washout were randomized after completing a 2-week single-blind placebo run-in period. In the 18-week study 521 patients were randomized and in the 24-week study 741 patients were randomized to the following treatment groups: placebo, sitagliptin 100 mg, or sitagliptin 200 mg. Those who failed to meet glycemic goals were treated with metformin rescue. In the 18-week study the A1C with sitagliptin 100 mg improved 0.6% over placebo and in the 24-week study the A1C improved 0.8% over placebo, both statistically significant with $p<0.001$. In the 18-week study FPG with sitagliptin 100 mg improved 20 points over placebo and in the 24-week study FPG improved 17 points over placebo, both statistically significant with $p<0.001$. In the 18-week study 9% of those on sitagliptin 100 mg required metformin rescue compared to 17% on placebo. In the 24-week study 9% of those on sitagliptin 100 mg required metformin rescue compared to 21% on placebo. sitagliptin 200 mg did not provide any greater glycemic effect than the 100 mg dose. sitagliptin lipid endpoints were similar to placebo. Body weight did not increase from baseline with sitagliptin.

A monotherapy safety study was conducted in 91 patients with type 2 diabetes and chronic renal insufficiency (eGFR < 50 ml/min). Those with moderate renal

insufficiency received a 50 mg daily dose of sitagliptin. Those with severe renal insufficiency, end stage renal disease on hemodialysis or peritoneal dialysis received 25 mg daily of sitagliptin. The safety and tolerability of sitagliptin was similar to placebo. There was a small increase in serum creatine in those with moderate renal insufficiency relative to placebo. Reductions in A1C and FPG seen with sitagliptin in chronic renal insufficiency were similar to those seen with sitagliptin in the other monotherapy studies.

Combination Studies

Sitagliptin has been studied in combination with other medications for the treatment of type 2 diabetes. Metformin doses ranging from 1000 mg per day up to 2000 mg per day have been evaluated with sitagliptin 100 mg daily resulting in an additional reduction in A1C of 0.7% to 2.1% compared to metformin alone.

Sitagliptin 100 mg has also been compared to glipizide (dose range 5 mg to 20 mg daily, mean 10 mg) as an add-on therapy for those inadequately controlled on metformin. The study findings indicate non-inferiority of sitagliptin to glipizide with A1C reduction of 0.5% for sitagliptin and 0.6% for glipizide. Of note, the rate of hypoglycemia was significantly higher with glipizide (32%) than with sitagliptin (4.9%) and those treated with sitagliptin had a reduction in body weight (-1.5 kg) compared to those treated with glipizide which had an increase in body weight (1.1 kg).

Sitagliptin 100 mg was studied in combination with glimepiride (4 mg or more per day) with or without metformin. Sitagliptin plus glimepiride resulted in an A1C reduction of 0.6% compared to the combination of sitagliptin, glimepiride and metformin which resulted in an A1C reduction of 0.9%. The rate of hypoglycemia was higher with sitagliptin in combination with glimepiride (12.2%) vs. glimepiride alone (1.8%).

Three studies evaluated sitagliptin as add on therapy with a TZD, either pioglitazone or rosiglitazone, the rosiglitazone study also included metformin in the treatment regimen. These studies showed significant reductions in A1C ranging from 0.7 to 0.9% compared to placebo. One of the studies reported more weight gain with the combination of sitagliptin + pioglitazone (3.0 kg) compared to pioglitazone alone (1.9 kg).

Sitagliptin has also been studied in combination with insulin. One study utilized pre-mixed, long-acting, or intermediate acting insulin with or without metformin. Those with inadequate glycemic control were randomized to sitagliptin 100 mg daily or placebo. The median change from baseline in daily dose of insulin was zero in both groups. The group with the addition of sitagliptin had an additional A1C decrease of 0.6% over placebo. An increased rate of hypoglycemia was noted in the group treated with the addition of sitagliptin compared to placebo. A second study utilized insulin glargine with metformin and those with inadequate glucose control were

randomized to either sitagliptin or placebo. After 30 weeks, the difference in sitagliptin over placebo in A1C reduction was 0.4%.

American Diabetes Association Treatment Guideline

Metformin is considered initial first-line treatment for type 2 diabetes unless there are contraindications to its use. The FDA has revised the labeling for metformin to reflect safety in those with eGFR 30 ml/min or greater. There is little systematic data available for other oral agents as initial therapy for type 2 diabetes. In those with contraindications or intolerance to metformin, initial therapy should be based on different clinical considerations. DPP-4 inhibitors (except saxagliptin in the setting of heart failure) are considered possible third-line options for those at high risk or have established ASCVD, CKD or HF. For those without these risks, DPP-4 inhibitors may be considered second-line to metformin use particularly for those with a compelling need to minimize hypoglycemia. Although DPP-4 inhibitors generally do not contribute to weight loss, they are considered weight neutral as opposed to sulfonylureas and insulin which may contribute to weight gain. In any circumstance, there is no benefit in adding a DPP-4 inhibitor to those that are already prescribed a GLP-1 RA.

Available DPP-4 Inhibitors:

- Januvia (Sitagliptin) 100 mg tab
- Onglyza (Saxagliptin) 2.5 mg or 5 mg tab
- Tradjenta (Linagliptin) 5 mg tab
- Nesina (Alogliptin) 25 mg tab

Special Considerations

- Once daily dosing without regard to meals
- Low risk for hypoglycemia as monotherapy
- Low risk for hypoglycemia in combination with metformin or TZD
- Evaluated for use in chronic renal insufficiency, adjusted dosing required for eGFR < 45 ml/min
- Considered weight neutral antidiabetic agent
- No added benefit then added to GLP-1 receptor agonist

Summary/Conclusion

Oral agents for type 2 diabetes approved for the formulary are limited to glipizide (sulfonylurea), metformin (biguanide), pioglitazone (TZD) and repaglinide (meglitinide). DPP-4 inhibitors may be considered for the treatment of type 2 diabetes in those who are intolerant or have contraindications to the first-line treatment, metformin, such as those with severe renal impairment. Since DPP-4 inhibitor monotherapy has a low risk for hypoglycemia, it may be considered for those at high risk for hypoglycemia. DPP-4 inhibitors can be prescribed as an add-on drug therapy for those inadequately controlled on metformin, TZD or sulfonylurea, although the risk for hypoglycemia is greater when combined with a sulfonylurea.

There is inadequate data to support DPP-4 inhibitor use with prandial insulin. Combination of a DPP-4 inhibitor with a GLP-1 receptor agonist does not provide additive glucose-lowering effects. Some of the DPP-4 inhibitors, saxagliptin and alogliptin, have been associated with an increased risk of heart failure resulting in hospitalization. DPP-4 inhibitors require dose adjustment in chronic kidney disease with the exception of linagliptin which is primarily eliminated via the enterohepatic system.

Recommendation

Addition of JANUVIA® (sitagliptin) to the formulary is recommended.

References

1. Product Information: JANUVIA® (sitagliptin). Merck & Co., Inc. Whitehouse Station, NJ, 2019.
2. American Diabetes Association. Glycemic Targets: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020 Jan;43(Supplement1): S66-76.
3. American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020 Jan;43(Supplement1): S98-110.
4. Dungan K, DeSantis A. Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus. UpToDate. Accessed 7/7/2020.

Prepared by:
Lisa M. Mican, Pharm.D., BCPP
Director of Pharmacy
Clinical Pharmacist
Austin State Hospital